

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.



February 11, 1999

Via Facsimile

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Director
Office of Pesticide Programs
Offices of Prevention, Pesticides,
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U.S. Environmental Protection Agency
401 M Street, S.W.
Mail Code 1119C
Washington, D.C. 20460

Re: Office of Pesticide Program's (OPP) Preliminary Risk
Assessment for Dichlorvos (Case No. 084001)

Dear Ms. Mulkey:

Amvac Chemical Corporation (Amvac) submits this letter to urge EPA not to issue publicly -- in the Office of Pesticide Program's (OPP) Public Docket, on the Internet, or otherwise -- OPP's Preliminary Risk Assessment for Dichlorvos (Case No. 084001) (Risk Assessment) until after it has considered key data and has corrected critical errors, in the current draft. Specifically, the Risk Assessment:

- Does not use, or even mention, a large body of studies directly relevant to DDVP toxicity and exposure -- studies on animal toxicity, human health effects, inter-individual variability and sensitive subpopulations, and exposure;
- Contains fundamental, critical errors that affect key conclusions; and

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- Misrepresents data upon which threshold conclusions are based.^{1/}

Before it properly can release the Risk Assessment to the public, EPA must review and incorporate the findings from these studies, correct the fundamental errors, and revise key data misinterpretations -- all of which significantly affect the entire Risk Assessment. These actions are essential for EPA to assess adequately, and in a scientifically sound manner, the potential risks posed by DDVP pesticides.

It also is inappropriate for EPA to release the Risk Assessment publicly because EPA has not provided Amvac with an adequate opportunity to comment on the Risk Assessment as a whole. Amvac was not timely provided with the documents on which the Risk Assessment relies. Amvac received some of those documents in the last week or so, and other documents only days ago. As discussed below, Amvac has not had an adequate opportunity to review the documents it has received, or to ascertain, based on that review, what other critical documents it does not have.

EPA's public release of the Risk Assessment in its current form will effectively function as a final agency regulatory decision, subject to judicial challenge. The availability of the Risk Assessment on the Internet is tantamount to issuing a cancellation notice without affording Amvac its statutorily guaranteed right of challenge. An analogous EPA action concerning second-hand smoke was expressly vacated when challenged in court for similar reasons,^{2/} as discussed below. EPA must, therefore, correct the errors here before releasing the Risk Assessment publicly.

Amvac requests an immediate meeting with you, Mr. Jack Housenger, Mr. Bob McNally, and any other EPA staff members you believe appropriate to discuss these important issues. Amvac wishes to work with EPA to ensure the significant flaws in the current Risk Assessment are corrected as expeditiously as possible.

^{1/} Amvac discusses in this letter only a few of the fundamental flaws in the Risk Assessment. There are a number of other significant issues not addressed here. Amvac in no way waives its rights to address these other issues -- many of which Amvac has raised previously -- in future submissions.

^{2/} *Flue-Cured Tobacco Co-op Stabilization Corp. v. EPA*, 4 F. Supp. 2d 435 (M.D.N.C. 1998).

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The Risk Assessment Ignores a Large Body of Studies

The Risk Assessment does not consider, or even mention, a large body of data on DDVP animal toxicity, human toxicity, inter-individual variability and sensitive subpopulations, and exposure. These data are critical to a scientifically sound Risk Assessment and must be incorporated before the Risk Assessment is released publicly.

Numerous Human Studies Are Not Considered

A large body of historical human data, much of which has long been in EPA's possession and/or the published literature, are completely absent from the Risk Assessment. Just a few examples of the human studies not even mentioned in the Risk Assessment are listed below; there are many others:

- Funckes, A.J., Miller, S., and Hayes, W. (1963). "Initial Field Studies in Upper Volta with Dichlorvos Residual Fumigant as a Malaria Eradication Technique." *Bull. Wld. Hlth. Org.* 29:243-246 (MRID Number 00048240).
- Gratz, N.G., *et al.* (1963). "A Village-Scale Trial with Dichlorvos as a Residual Fumigant Insecticide in Southern Nigeria." *Bull. Wld. Hlth. Org.* 29:251-2701 (MRID Number 00060481).
- Leary, J.S., *et al.* (1974). "Safety Evaluation in the Homes of Polyvinyl Chloride Resin Strip Containing Dichlorvos (DDVP)." *Arch. Environ. Health* 29:308-314.
- Menz, M.H., *et al.* (1974). "Long-Term Exposure of Factory Workers to Dichlorvos (DDVP) Insecticide." *Arch. Environ. Health* 28:72-76 (MRID Number 00118117).
- Slomka, M.B. and Hine, C.H. (1981). "Clinical Pharmacology of Dichlorvos." *Acta Pharmacol. Et Toxicol* 49:105-108.

The human database includes studies that were designed specifically to look for early signs of cholinesterase inhibition, such as pupillary reactivity and visual acuity. Most of the studies include the documentation of subjective symptoms, as well as clinical assessments of any abnormal

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changes, including measurements of cholinesterase in red blood cells (RBCs) and plasma. Certain studies made other physiological measurements to assess cardiac, neurological, lung, and kidney function. These studies -- and other reports not considered in the Risk Assessment -- show that high exposures to DDVP, either orally or by inhalation, are not toxic for healthy humans. EPA cannot release publicly a Risk Assessment that does not consider this large body of significant data.

Numerous Animal Data Are Not Considered

There is also a significant body of data on DDVP's potential cholinesterase inhibition effects in a variety of species, including monkeys and other laboratory animals, that EPA does not consider in the Risk Assessment. Just a few examples of the missing studies are listed below; many others exist:

- Hass, K.D., Collins, J.A., and Kodama, J.K. (1972). "Effect of Orally Administered Dichlorvos in Rhesus Monkeys." *JAVMA* 161:714-719.
- Walker, A.I.T., Blair, D., Stevenson, D.E., and Chambers, P.L. (1972). "An Inhalational Toxicity Study with Dichlorvos." *Arch. Toxicol.* 30:1-7 (MRID Number 00063562).
- Durham, W.F., Gaines, Th.B., McCauley, R.H., Jr., Sedlak, V.A., Mattson, A.M., & Hayes, W.J., Jr. (1957). Studies on the toxicity of 0,0-dimethyl-2,2-dichlorovinyl phosphate (DDVP). *Am. Med. Assoc. Arch. Ind. Health*, 15:340-349.

These -- and numerous other well-controlled animal studies -- contain repeated measurements of cholinesterase effects. Yet, the Risk Assessment does not address them.

Critical Data on Inter-Individual Variability and Sensitive Subpopulations Are Not Considered

Likewise, the Risk Assessment ignores critical data on inter-individual variability and sensitive subpopulations. Just a few examples are listed below; many others exist:

- Cavagna, G., Locati, G., and Vigliani, E.C. (1970). "Exposure of Newborn Babies to Vapona Insecticide." *European J. of Toxicol.* 11:49-57 (MRID Number 00056187).

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- Cavagna, G., Locati, G., and Vigliani, E.C. (1969). "Clinical Effects of Exposure to DDVP (Vapona) Insecticide in Hospital Wards." *Arch Environ Health* 19:112-123 (MRJD Number 00060476).
- Chavarria, A. Pcna, Swartzwelder, J.C., Villarejos, V.M., Kotcher, E., and Arguedas, J. (1969). "Dichlorvos, an Effective Broad - Spectrum Anthelmintic." *The American Journal of Tropical Medicine and Hygiene* 18(6):907-911.
- Cervoni, W.A., Oliver-Gonzalez, J., Kaye, S., and Slomka, M.B. (1969). "Dichlorvos as a Single - Dose Intestinal Anthelmintic Therapy for Man." *The American Journal of Tropical Medicine and Hygiene* 18(4):912-919.

The majority of the data on exposed sensitive subpopulations show little to no effects from exposures to DDVP. Children exposed to DDVP in hospital pediatric wards in Italy (Cavagna *et al.* 1969) showed no unfavorable effects. Similar results were seen in diseased adults (Cavagna *et al.* 1969) and in very sick adults (Chavarria *et al.* 1969; Cervoni *et al.* 1969). The studies demonstrate there is little inter-individual variability from exposure to DDVP. The Risk Assessment cannot properly ignore these important data, and the many other similar studies available.

Critical Exposure Data Are Not Considered

Similarly, significant data on exposure are not considered in the Risk Assessment. Just a few examples are listed below; many others exist:

- Deer, H.M., Beck, E.D., and Roe, A.H. (1993). "Respiratory Exposure of Museum Personnel to Dichlorvos Insecticide." *Vet Hum Toxicol* 35 (3):226-228.
- Elgar, K.E., and Steer, B.D. (1972). "Dichlorvos Concentrations in the Air of Houses Arising from the Use of Dichlorvos PVC Strips." *Pestic Sci.* 3:591-600.
- Elgar, K. E.; Mathews, B.L., and Bosio, P. (1972). "Vapona Strips in Shops -- Residues in Foodstuffs." *Environ. Qual. Safety* 1:217-221.

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- Leary, J. S., Keane, W.T., Fontenot, C., Feichmeir, E.F., Schultz, D., Koos, B.A., Hirsch, L., Lavor, E.M., Roan, C.C. and Hine, C.H. (1974). "Safety Evaluation in the Home of Polyvinyl Chloride Resin Strip Containing Dichlorvos (DDVP)." *Arch Environ. Health* 29:308-314.

These studies, which focus on exposure to pest strips, and others, which examine exposure to pest strips and other DDVP uses, must be considered in the exposure review. For example, the studies by Elgar and Steer (1972) and Leary *et al.* (1974) demonstrate the low concentrations of DDVP measured during pest strip use. It is inappropriate, given the wealth of available data not considered, to rely on a single study to estimate exposure. Only by considering all of the data will EPA be able to incorporate into the Risk Assessment the variability in exposure due to the real-world differences in exposure conditions.

The DDVP Risk Assessment Contains Fundamental, Critical Errors

There Are Clear and Significant Errors in EPA's Exposure Calculations

The Risk Assessment contains fundamental mathematical errors in the exposure calculations. The Risk Assessment is based on the exposure numbers in the Jaquith 1998h memorandum (Revision of Exposures from Dichlorvos (DDVP) Resin Strips). Table 1 of the Jaquith memorandum presents the concentrations used in the risk assessment and the resulting margins of exposure (MOEs). The concentrations presented as "AUC/120 days" are intended to represent the time-weighted average concentrations for the use of the pest strips. These concentrations are higher than the concentrations measured at any time during the study. Clearly, this cannot be correct. Specifically, the mean concentration can be calculated to be $0.32 \mu\text{g}/\text{m}^3$. The highest measured concentration in the study was $0.11 \mu\text{g}/\text{m}^3$, however. This significant error must be corrected.

Additionally, the MOEs listed in the Jaquith document are not the values presented in Table 16 of the "Preliminary HED Risk Assessment for Dichlorvos." Thus, it is not possible to determine if additional mathematical errors were made in the estimation of the MOEs presented in the Risk Assessment. A document with such fundamental errors and lack of transparency cannot be released to the public.

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***EPA's Calculations Based
On the Blair et al. Study Are Incorrect***

EPA grossly misrepresents the dose received by inhalation in the Blair *et al.* rat study,^{2/} which is the basis for EPA's assessment of the chronic inhalation risks posed by DDVP. The animals were exposed to DDVP by a number of routes in addition to inhalation. Specifically, the total dose received by the animals is the total of the inhaled dose, material licked off the fur after continual deposition from the air, material deposited in the water, material ingested from deposition on food, and material absorbed through the skin. In addition, because food and water were offered *ad libitum* and changed only twice a week, a significant opportunity existed for contamination of both the food and water with DDVP, thus increasing the dose of DDVP to which the animals were exposed orally.

Data are available to estimate exposure from routes other than inhalation. EPA failed to perform calculations to determine the actual inhaled dose, and instead attributed all of the biologic effects to the inhaled dose. This is a significant mathematical error and grossly misrepresents the dose of DDVP to which the rats were exposed via inhalation. The no observed effect level (NOEL) for exposure from the inhalation route alone should have been much higher -- and the MOEs calculated from these data much larger -- than those stated in the Risk Assessment.

In fact, the study authors, clearly aware that the dose the animals received was far greater than just the dose inhaled, commented that the total intake of DDVP in the study by other routes of exposure was twice the intake by the inhalation route;^{4/} studies in the literature with DDVP and other substances indicate that this error is much larger.^{2/} The Blair *et al.* study authors explicitly

^{2/} Blair, D., *et al.* (1976) "Dichlorvos -- A 2-Year Inhalation Carcinogenesis Study in Rats." *Arch. Toxicol.* 35:281-294.

^{4/} Blair *et al.* (1976) at 292. ("[U]nder the conditions of the test, the total intake of dichlorvos, on a mg/kg basis, by the various routes is twice the intake via the inhalation route alone.")

^{2/} See, e.g., Cochran, R.C., Formoli, T.A., Pfeifer, K.F., and Albous, C.N. (1997). "Characterization of risks associated with the use of molinate." *Regulatory Toxicol. Pharmacol.* 25:146-156; Stevenson, D.E. and Blair, D. (1977). "The uptake of dichlorvos during long-term inhalation studies." *Proc. Eur. Soc. Toxicol.* 18:215-217.

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stated that the total exposures in the rat study were much higher than the inhalation exposure to humans under similar DDVP atmospheric conditions:

As a consequence of this additional intake via other routes and the high respiratory minute volume per kg body weight in rats compared with man, the total exposures were undoubtedly much greater in all three treatment groups than the inhalation exposure of larger animals and man to similar atmospheric concentrations of dichlorvos.^{6/}

EPA failed to take this critical information into account in its Risk Assessment. EPA must fairly estimate the inhaled dose of DDVP the animals received and must correct the inhalation risk assessments. The current Risk Assessment vastly misrepresents the inhalation exposure from the rat study.

The Risk Assessment Misinterprets Critical Data

EPA's principal concern with DDVP pesticide use is potential cholinesterase inhibition.^{7/} EPA based its assessment of the long-term risks posed by DDVP on Blair *et al.* (1976) -- a rat inhalation chronic carcinogenicity study that cannot properly be used to assess cholinesterase inhibition. The study was designed specifically to investigate the carcinogenic potential of DDVP, and not as a chronic toxicity study, or even a combined study. There were insufficient animals allocated to the study design to support the required evaluations of a chronic toxicity study, so the determination of a no effect level for cholinesterase inhibition from this limited data set is totally unwarranted. The authors themselves state that "[t]he primary aim of this inhalation study was to investigate the effects, if any, on tumor incidence in animals exposed for their lifetime to test atmospheres containing dichlorvos."^{8/}

^{6/} Blair *et al.* (1976) at 292.

^{7/} Risk Assessment at 3.

^{8/} Blair *et al.* (1976) at 283.

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In the Blair *et al.* study, rats were exposed to DDVP for 23 hours/day, 7 days/week at concentrations of 0, 0.05, 0.5, and 5 mg/m³ for two years -- essentially the animals' lifetime. Cholinesterase measurements were not made prior to exposure or during the course of the study. Without a baseline for cholinesterase values, and monitoring throughout the course of the study, single measurements at the end of the study have little scientific meaning or validity as a measure of chronic toxicity.

Moreover, only a single cholinesterase determination was taken on the few surviving animals at the end of the two-year study. This resulted in measuring cholinesterase in very old animals at one time point. Yet, no treatment-related differences were seen in acetylcholine measurements on the brain tissue after two years of exposure, and no signs of cholinesterase inhibition were observed throughout the lifetime of the animals, despite the fact that the authors were specifically looking for these effects.^{2/}

In addition, exposure to DDVP increased the survival of both male and female rats. Comparatively, fewer control animals survived. Therefore, more animals in the treated groups were available for cholinesterase determinations. For example, for the males, cholinesterase measurements were only taken for 8 control animals, 18 low dose animals, 12 mid-dose animals, and 29 high dose animals. This inequality of test groups confounds the analysis because it limits the confidence that can be placed in the results. In short, the limited number of animals measured for cholinesterase levels, the comparatively small number of controls measured, the use of geriatric animals, and the absence of cholinesterase monitoring throughout the course of the study renders this study of very little value for determining the impact of DDVP on chronic cholinesterase activity.^{10/}

^{2/} Indeed, the authors noted that "in acute exposure to organophosphorous compounds there is a good correlation between brain acetylcholine concentration and depression of brain cholinesterase activity." Blair *et al.* (1976) at 292-293. The authors continued: "[i]t was, therefore, of particular interest to note this relationship was not found after 2 years' exposure." *Id.* at 293. Accordingly, the authors concluded that the small change in the mean RBC cholinesterase value in the 0.05 mg/m³ female group was "too small a change to be of toxicological significance." *Id.*

^{10/} Information in the literature demonstrates that equilibrium for cholinesterase inhibition is achieved relatively rapidly from repeat exposures to DDVP. See, e.g., Durham, W.F., Gaines, Th.B., McCauley, R.H., Jr., Sedlak, V.A., Mattson, A.M., and Hayes, W.J., Jr. (1957). "Studies on the toxicity of 0,0-dimethyl-2,2-dichlorovinyl phosphate (DDVP)." *Am.*

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**Given These Omissions, Errors, and Misrepresentations, EPA
Cannot Legally Release the Risk Assessment Publicly**

The Law Requires EPA to Consider All Relevant Data

It is well-settled that a government agency must base its decision-making on a consideration of all relevant factors -- in this case, the large body of existing human, animal, and exposure data that the Risk Assessment fails to address or even mention.^{11/} Courts have repeatedly overturned federal agency decisions where the agency refused to consider significant information. For example, in a case analogous to the fact situation here, the United States Court of Appeals for the Fifth Circuit found that the Consumer Product Safety Commission's (CPSC) exclusive reliance on a rat study inadequate to support its rule where the CPSC failed to consider a body of available epidemiology studies.^{12/} In failing to consider the large human and animal database on DDVP, EPA has failed to meet its legal obligation here and cannot, for this reason, release the Risk Assessment publicly.^{13/}

Med. Assoc. Arch. Ind. Health 15:340-349. This is an important consideration for risk assessment. The absence of measurements during the course of the rat study precluded any assessment of equilibrium considerations.

^{11/} See, e.g., *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402 (1971); *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29 (1983).

^{12/} *Gulf S. Insulation v. CPSC*, 701 F.2d 1137, 1146 (5th Cir. 1983); see also *Public Citizen Health Research Group v. Tyson*, 796 F.2d 1479, 1497 (D.C. Cir. 1986) ("We demand no more than that the agency arrive at a reasonable conclusion based on all the evidence before it."); *id.* at 1507 (Court remanded case to OSHA for failure to set STEL on grounds that OSHA's deliberations on this issue were incomplete and OSHA had "entirely failed to consider an important aspect of the problem...").

^{13/} Amvac notes in this regard that, in addition to ignoring the large body of existing study data, the Risk Assessment fails to consider the report of a preeminent body of scientists considered by Amvac expressly to address EPA concerns (Blue Ribbon Panel). With a "back of the hand" attitude, EPA states in the Risk Assessment:

The DDVP Registrant has conducted an independent peer review of the cholinesterase endpoint for DDVP by a Blue Ribbon Panel of

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This is particularly true given that, in ignoring the large body of data on human toxicity, animal toxicity, inter-individual variability and sensitive subpopulations, and exposure, EPA has acted in a manner contrary to its own regulations, policy, and precedent. EPA's risk assessment guidelines follow a "total weight of the evidence" approach, which is based upon all available, reliable data and information, not on any single analysis or theory.^{14/} EPA has not

Experts. The conclusions of the Blue Ribbon Panel were presented orally at the July 1998 SAP. The Agency has not yet had an opportunity to review the Blue Ribbon Panel Report.

Risk Assessment at 53. This statement is made despite the fact that the Panel made conclusions directly relevant to the Risk Assessment. Specifically, the Blue Ribbon Panel concluded that the available human data reduce, if not eliminate, the need to rely on clinical signs obtained in animals or other even less predictive measures. Based on the human data, the Blue Ribbon Panel reached the following conclusions:

- Existing human data support an acute NOEL of 1.0 mg/kg.
- Existing human data support a chronic NOEL of 0.1 mg/kg for cholinesterase alteration.
- Controlled clinical trials on metrifonate, a compound which converts to DDVP, have demonstrated the safety of maintaining humans at continually reduced RBC cholinesterase levels (50-75 percent) for periods in excess of six years.

Final Report of the Expert Panel -- An Evaluation of the Significance of Dichlorvos Induced Alterations of Cholinesterase Levels in Biological Systems (Nov. 13, 1998) at 49 and 50.

^{14/} This weight-of-the-evidence approach is consistent throughout EPA's risk assessment guidelines. For example, in its Guidelines for the Health Assessment of Suspect Developmental Toxicants, EPA states: "[T]he guidelines emphasize that risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information. This case-by-case approach means that Agency experts review the scientific information on each agent and use the most scientifically appropriate interpretation to assess

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articulated any sound basis here for radically departing from its well-established weight-of-the-evidence approach and ignoring these important data in its Risk Assessment. It is a fundamental principle of administrative law that an agency must follow its own precedents, absent a rational explanation for departure from such precedent.¹⁹ EPA's attempt here to ignore the highly relevant body of animal and human data is clearly contrary to EPA precedent and formal policies.

Indeed, EPA's present policy on the use of data on cholinesterase inhibition for risk assessments explicitly requires a consideration of all animal and human data, *giving precedence to available human data*. EPA states:

A weight of the evidence approach for evaluation of any ChE inhibitor should consider all of the available data from animal and human studies, and human exposures to identify the hazards and the exposure levels at which they occur. First the individual studies are evaluated, then all studies and their relation to one another are examined in concert.

risk. The guidelines also stress that this information will be fully presented in Agency risk assessment documents, and that Agency scientists will identify the strengths and weaknesses of each assessment by describing uncertainties, assumptions, and limitations, as well as the scientific basis and rationale for each assessment." 51 Fed. Reg. 34028 (Sept. 24, 1986).

¹⁹ See *Vitarelli v. Seaton*, 359 U.S. 535, 539-40 (1959); *National Conservative Political Action Comm. v. FEC*, 626 F.2d 953, 959 (D.C. Cir. 1980) ("Agencies are under an obligation to follow their own regulations, procedures, and precedents, or provide a rational explanation for their departures."); *Northwest Airlines, Inc. v. U.S. Dep't of Transp.*, 15 F.3d 1112, 1121 (D.C. Cir. 1994) ("An Agency should not gloss over or swerve away from prior precedent without discussion."); *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970), *cert. denied*, 403 U.S. 923 (1971) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.") (citation omitted); *Western States Petroleum Ass'n v. EPA*, 87 F.3d 280, 284 (9th Cir. 1996) ("EPA 'may not depart, sub silentio, from its usual rules of decision to reach a different, unexplained result in a single case.'") (citation omitted).

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Typically, a critical effect level is selected for a route and duration of exposure that represents the most sensitive effect seen. Based on considerations of the weight of the evidence from all of the studies as a group, this level may or may not be the lowest one in which an effect was seen. *Valid and reliable human data, when available, take precedence.*^{16/}

EPA emphasized that the risk characterization must be based on a broad evaluation of the pattern of observed toxicity, including such factors as the "relationship between exposures and different effects," "the nature and severity of effects seen; the slope of the dose effect curves for different effects, and the completeness of the effects evaluated."^{17/} Other factors that EPA identified as "important to consider in the total data base" include "the number of human incidents reported, and the scope of the effects evaluated."^{18/} Finally, EPA stated that "the strengths and weaknesses in the data base should be summarized and the uncertainties in defining the critical effects should be clearly documented."^{19/}

EPA has ignored its own requirements in preparing the Risk Assessment. It thus cannot release the Risk Assessment publicly.

^{16/} Office of Pesticide Programs, Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides (Oct. 27, 1998) at 14 (Science Policy Document), <<http://www.epa.gov/oppfead1/trac/sciencce/index.htm>> (PDF format).

^{17/} *Id.* at 16.

^{18/} *Id.*

^{19/} *Id.*

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***EPA Cannot Legally Ignore Exposure and Incidence Data and Rely
Instead on Faulty Assumptions or Predictions***

The Scientific Advisory Panel (SAP) concluded at its July 29-30, 1998, meeting that all of EPA's proposed models for exposure assessment for the pest strips are seriously flawed, and recommended that EPA request additional data from Amvac.^{20/} The Panel stated in this regard:

[B]etter knowledge of real world use practices would serve to improve residential exposure analyses, and . . . the lack of knowledge about actual use (and misuse) for such consumer products as resin strips is an important area of uncertainty in residential exposure analysis. The Panel encourages the Agency and registrants to consider collecting such data to improve estimates of residential exposures.^{21/}

There are significant existing exposure data that EPA has not considered, however, as outlined above. After EPA has reviewed these existing studies, Amvac is willing to develop and submit any additional data that might be needed to provide knowledge about exposures from current uses.

Likewise, it is significant that there has been no "countable" disease incidence from the use of the DDVP pest strips. The disease incidence data provided by EPA include no data specific to pest strips.^{22/} This belies the MOEs presented by EPA. EPA must, as part of performing the Risk Assessment, consider data showing the lack of disease incidence over time. This is an important part of a human risk assessment and cannot be ignored. It is a simple, but useful, reality check of EPA's Risk Assessment, and is a clear signal that EPA's calculations are not correct.

^{20/} Scientific Advisory Panel (SAP) Meeting -- July 1998 Final Report (Sept. 2, 1998) at 24-26, <<http://www.epa.gov/pesticides/SAP/july/finaljul.htm>>.

^{21/} *Id.* at 26.

^{22/} Risk Assessment at 19-24.

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Here, the MOEs are wholly inconsistent with the data. For example, studies in healthy humans have shown that DDVP is not acutely toxic under typical exposure conditions (e.g., exposure to a resin strip under label conditions, exposure to a home that has been fogged after proper ventilation). In all short-term exposure studies in humans, physiological test results have been normal, and there have been no reported signs or symptoms of toxicity (Hunter 1969; Ueda and Nishimura 1967; Hunter 1970b).^{22/} Additionally, at air concentrations higher than typical exposure levels, plasma cholinesterase has been unaffected or inhibited only moderately, and RBC cholinesterase inhibition has not been clearly demonstrated (Hunter 1969).

EPA itself emphasized in its cholinesterase policy document the importance of considering in the total database the "number of human incidents reported, and the scope of the effects evaluated."^{24/} Yet, no such considerations are included in EPA's Risk Assessment.

It is arbitrary, and not consistent with EPA's legal obligations, for EPA to release the Risk Assessment, with full knowledge that: (1) the models used for its exposure assessment are flawed and fraught with uncertainties; (2) a significant portion of the database has been ignored in the assessment; and (3) actual data completely contradict the predictions EPA makes based on faulty assumptions. EPA has an obligation to conduct a risk assessment using real-world exposure levels, not hypothetical exposures.^{25/}

^{22/} Hunter, C.G. (Tunstall Laboratory) (1969). Report on initial studies of deliberate exposures to high concentrations of dichlorvos by human subjects (MRID Number 00060484); Ueda, K. and Nishimura, M. (1967). Effect of Vapona/Strips to Human Beings (MRID Numbers 00048262, 00049987); Hunter, C.J. (Tunstall Laboratory) (1970b). Dichlorvos: Inhalation exposures with human subjects. Part 2.

^{24/} Science Policy Document at 16.

^{25/} See, e.g., *Gulf S. Insulation v. CPSC*, 701 F.2d at 1148 (Court found that the Commission's finding that urea-formaldehyde foam insulation (UFFI) poses an unreasonable risk of injury from acute irritant effects was not supported by substantial evidence because the Commission failed to quantify the risk at the exposure levels actually associated with UFFI).

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EPA Has Unlawfully Deprived Amvac of Its Notice and Comment Rights

EPA has denied Amvac adequate time to comment on the Risk Assessment. On January 13, 1999, Amvac notified EPA that it had not received all the materials referenced in the Risk Assessment. EPA subsequently provided some, but not all, of the missing references of which it was then aware. These are listed in Attachment 1. Amvac submitted another letter to EPA on February 5, 1999, requesting those missing references. Amvac received on February 9, 1999 -- only two days ago -- the specific references it requested.²⁶

Moreover, and as Amvac's February 5, 1999, letter notes, many of the listed references rely on EPA documents that are not included on the reference list and that are not available to Amvac. In the brief time Amvac has had to review the documents it has now received from EPA, Amvac has deemed that the following additional references, listed in the Jaquith memoranda that EPA provided on February 2, 1999, are needed:

- Van Kampen, K.R., Brooks, D.R., and Allen, S.D. (1977). Influence of High Temperature and Low Humidity on Cats Wearing Single and Multiple Dichlorvos Flea Collar. Shell Chemical Company. (Referenced in Jaquith (1998c) and Jaquith (1998i) #4.)
- Memorandum from D. Jaquith (EAB) to C. Monroe (SIS) titled "Exposure of Cats and Dogs to DDVP from Flea Collar Use" (Aug. 11, 1987). (Referenced in Jaquith (1998c) and Jaquith (1998i) #2.)
- Memorandum from D. Jaquith (OREB) to D. Utterback (SRB) titled "Assessment of Exposure of Residents to DDVP Applied as a Total Release Fogger" (May 10, 1993). (Referenced in Jaquith (1998k) and Jaquith (1998m) #4.)
- Memorandum from D. Jaquith (CEB2) to C. Scheltema (RCAB) titled "Revised Exposures to Dichlorvos (DDVP) Resulting from Dairy Barn and Animal Spray Uses (PC Code 084001, Barcode 251330)" (Dec. 3, 1998).

²⁶ Amvac notes that it received only every other page of one of the requested references: Tarplee, B. and Rowland, J. (1988). "Dichlorvos (DDVP) - Report of the FQPA Safety Factor Committee" (June 2, 1998).

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Currently undergoing internal HED Review. (Referenced in Jaquith (1998i).)

- Memorandum from J. Arthur (EXPOSAC Chair) to D. Jaquith (CEB2) titled "Review of DDVP Exposure Assessment for Scenarios: Total Release Fogger; Turf; Aerosol Crack/Crevise Treatment, and Pet Collars" (Aug. 31, 1998.) (Referenced in Jaquith (1998j), Jaquith (1998k) #3, and Jaquith (1998m) #3.)
- Memorandum from M. Dow (BUD) to D. Pilitt (RD) titled "DDVP (Vapona) QUA" (Oct. 2, 1985). (Referenced in Jaquith (1998l) (which is actually dated January 27, 1999, rather than November 1998 and Jaquith (1998n).)
- PHED Surrogate Exposure Guide (May 1997). (Referenced in Jaquith (1998l) and Jaquith (1998n).)

All of these documents are critical to a meaningful and complete review of the Risk Assessment. As Amvac has stated in its prior correspondence on this issue, Amvac cannot adequately comment on the Risk Assessment without all information on which the Risk Assessment relies, and the 30-day comment thus cannot properly begin until Amvac has received all of these documents.

Moreover, three of the Jaquith memoranda (1998l, 1998m, and 1998n) have January 1999 dates, indicating that changes may have recently been made to those support documents. Because these three support documents are dated after the December release of the Risk Assessment for comment to Amvac, it is possible that there may have been changes in the support documents that are not reflected in the Risk Assessment. Amvac has not been given an adequate opportunity to review these documents and determine if any changes in the support documents are reflected in the Risk Assessment.

In short, EPA cannot lawfully release the Risk Assessment to the public without allowing Amvac a 30-day opportunity to comment on all the information underlying the Risk Assessment. It is a clear violation of due process to present an alleged finding as an agency decision where an inadequate opportunity to comment was provided.²⁷

²⁷ See, e.g., *Grossman v. Axelrod*, 466 F. Supp. 770, 775 (S.D.N.Y. 1979), *aff'd* 646 F.2d 768 (2d Cir. 1981); *Synthetic Organic Chem. Mfrs. Ass'n v. Brennan*, 506 F.2d 385, 388-89 (3d

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EPA's Release of the Risk Assessment Will Effectively Function as a Final Decision and Deprive Amvac of Its Rights Without Due Process of Law

The Risk Assessment -- if released publicly in its present form -- will effectively function as a final agency regulatory decision, subject to judicial challenge, as far as Amvac's registration of the DDVP pest strips is concerned. The public release of the Risk Assessment will send a clear message to the world that the DDVP pesticide products pose too great a risk to warrant continued registration. Viewers of the EPA web site will reasonably conclude that EPA has taken final action and that cancellation of the pest strips and other DDVP products is imminent.

A recent case addressing a challenge to an EPA risk assessment for second hand smoke demonstrates that EPA cannot release the Risk Assessment under these circumstances. The assessment at issue in that case was not a part of any formal rulemaking activity, but was contained in a final EPA report. Nonetheless, the risk assessment was subject to court review.^{28/} The court

Cir. 1974), *cert. denied sub nom., Oil, Chem. & Atomic Workers Int'l Union*, 423 U.S. 830 (1975) (Court remanded standards to the Department of Labor where the agency did not give interested parties adequate time to comment because it published a proposed rule before the advisory committee submitted its final report on the rule.) *See also Chemical Waste Management, Inc. v. E.P.A.*, 976 F.2d 2, 28 (D.C. Cir. 1992), *cert. denied sub nom., Chemical Mfrs. Ass'n v. EPA*, 507 U.S. 1057 (1993); *Florida Power & Light Co. v. United States*, 846 F.2d 765, 771 (D.C. Cir. 1988), *cert. denied*, 490 U.S. 1045 (1989) (agency must "provide sufficient factual detail and rationale for the rule to permit interested parties to comment meaningfully."); *Horsehead Resource Dev. v. Browner*, 16 F. 3d 1246, 1267-68 (D.C. Cir.), *cert. denied sub nom., Cement Kiln Recycling Coalition v. Browner*, 513 U.S. 816 (1994). While these cases address the requirement for notice and comment in the context of rulemaking, the principles are equally applicable to the issuance of a risk assessment -- such as the Risk Assessment -- which has the *de facto* effect of a final agency action.

^{28/} *Flue-Cured Tobacco Co-op Stabilization Corp. v. EPA*, 4 F. Supp 2d at 443 ("EPA's activities did not amount to formal regulation, for it issued no regulations and made no attempt to directly manage ETS risks. EPA's activities constituted *de facto* regulatory activity . . ."). Amvac notes that in the second hand smoke case, EPA argued that it could base its risk assessment on certain human data because "[t]he use of human evidence eliminates the uncertainties that normally arise when one has to base hazard identification

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vacated the risk assessment, finding that EPA had violated its procedural requirements and precedent, failed to include the entirety of the database in its risk assessment, and acted improperly to try to restrict the Plaintiff's products and influence public opinion:

EPA publicly committed to a conclusion before research had begun; excluded industry by violating the Act's procedural requirements; adjusted established procedure and scientific norms to validate the Agency's public conclusion, and aggressively utilized the Act's authority to disseminate findings to establish a de facto regulatory scheme intended to restrict Plaintiff's products and to influence public opinion. In conducting the ETS Risk Assessment, EPA disregarded information and made findings on selective information; did not disseminate significant epidemiologic information; deviated from its Risk Assessment Guidelines; failed to disclose important findings and reasoning; and left significant questions without answers.^{29/}

EPA's public release of the Risk Assessment here is similarly flawed. EPA is publicly committing to a conclusion that will significantly restrict Amvac's products and influence greatly -- and irreparably -- public opinion without considering available data, and in violation of important procedural requirements. In essence, the availability of the Risk Assessment on the Internet is tantamount to issuing a cancellation notice without affording Amvac its statutorily guaranteed right of challenge. Adverse publicity in the newspapers and on television, among other media, is inevitable. Consumers will cease to purchase and use the Amvac DDVP products. As a

on the results of high-dose animal experiments." *Id.* at 454.

^{29/} *Id.* at 466. See also *id.* at 463, where the court criticized EPA's methodology as one developed to support a pre-determined conclusion. The court stated: "Using its normal methodology and its selected studies, EPA did not demonstrate a statistically significant association between ETS and lung cancer. This should have caused EPA to reevaluate the inference options used in establishing its plausibility theory. A risk assessment is supposed to entail the best judgment possible based upon the available evidence. . . . Instead, EPA changed its methodology to find a statistically significant association. EPA claimed, but did not explain how, its theory justified changing the Agency's methodology" (citation omitted).

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result, Amvac will suffer lasting and irreparable loss of sales, with significant adverse consequences to its business interests.

Even if EPA ultimately revises the Risk Assessment, as Amvac believes it should, the damage cannot be undone. Consumers will be unwilling to purchase a product that has been branded as unsafe, however erroneously. This is human nature. Lingered for many years in the minds of consumers will be the message that the pest strips and other DDVP products pose a risk, as conveyed by news reports, television specials, and advertising by Amvac's competitors. A potential publicity campaign against Amvac by competitors and environmentalist groups -- a logical outcome of the public availability of the Risk Assessment -- will not only lead to the effective loss of the pest strip and other DDVP products for Amvac, but will also create ill will towards Amvac and potentially affect the acceptance and sales of its other products, both here and abroad. These are the inevitable adverse consequences if EPA releases a risk assessment based on flawed premises.^{20/}

In fact, Amvac has experienced precisely these effects with its DDVP products in the past, when EPA erroneously classified DDVP as a Group B2 probable human carcinogen. That classification caused a loss of approximately 90 percent of the DDVP market. EPA later changed the Group B2 classification to a Group C possible human carcinogen classification, and even the Group C classification is based on a study for which EPA's SAP found that there is "compelling evidence" that it is not relevant for human risk assessment.^{21/} Moreover, even with the change in classification and significant data showing that carcinogenicity is not a concern for DDVP, the stigma of the original, erroneous B2 classification remains.

The interest of the public in scientifically sound and rational governmental decision-making will also be harmed by EPA's proposed action. Public policy dictates that the public should not be falsely alarmed by a government agency about the risks posed by a consumer product where the agency's risk assessment is not scientifically valid.

* * * * *

^{20/} See, e.g., *Dow Chem. v. CPSC*, 459 F. Supp. 378, 395 (W.D. La. 1978).

^{21/} SAP, *Federal Insecticide, Fungicide and Rodenticide Act, Scientific Advisory Panel Meeting, A Set of Scientific Issues Being Considered by the Agency in Connection with DDVP (Dichlorvos) Risk Issues* (SAP Report) (Sept. 2, 1998) at 17.

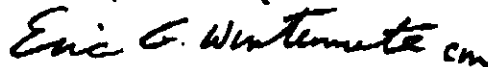
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Because of the magnitude of the harm that is likely to ensue if EPA releases its faulty Risk Assessment to the public, Amvac strongly urges EPA to: (1) review and incorporate into the Risk Assessment studies that are now wholly absent from it; (2) correct critical errors in the Risk Assessment; and (3) revise the significant misinterpretations of data that are discussed in the Risk Assessment. Moreover, EPA must give Amvac an adequate opportunity to comment on the Risk Assessment. Only after EPA takes these actions should EPA publicly release the Risk Assessment.

The current Risk Assessment is built on a faulty and incomplete foundation. In the interest of fairness, due process, and good science, EPA must not place its highly erroneous Risk Assessment in its public docket or on the Internet.

Amvac requests an immediate meeting with you, Mr. Jack Housenger, Mr. Bob McNally, and any other EPA staff members you believe appropriate to discuss these important issues. Amvac wishes to work with EPA to ensure the significant flaws in the current Risk Assessment are corrected as expeditiously as possible.

Sincerely,

Handwritten signature of Eric G. Wintemute in cursive script.

Eric G. Wintemute
President

Attachment

cc: Mr. Jack E. Housenger (w/attachment) (via facsimile)
Mr. Robert C. McNally (w/attachment) (via facsimile)

Blondell, J. and Spann, M. (1998). "Review of DDVP Incidence Reports." DP Barcode D242971. Chemical # 084001. Reregistration Case # 0310 (Mar. 31, 1998).

Dannan, G. (1998). "Toxicology Review for Reregistration Eligibility Document on Dichlorvos (DDVP)" (Feb. 20, 1998).

Ghali, G. (1997). "Dichlorvos (DDVP): Hazard Identification Committee Report" (Dec. 19, 1997).

Hummel, S. (1998a). "Dichlorvos (0804001) Special Review: Response to PD 2/3 and Anticipated Residues for Dichlorvos Resulting from the Use of Dichlorvos, Naled, and Trichlorfon" (Apr. 9, 1998).

Hummel, S. (1998b). "Dichlorvos (084001). Anticipated Residues for Dichlorvos Resulting From Use of Dichlorvos and Naled" (June 15, 1998).

Jaeger, R. (1989). Transmittal of the Final FIFRA Science Advisory Panel Report on the September 28-29 Meeting. Memo to D. Camp (Oct. 16, 1989).

Kent, R. (1998). Personal Communication (e-mail) to C. Scheltema. DDVP-Application of Inhalation Endpoint (Nov. 20, 1998).

Lewis, P. (1998). Transmittal of the Final Report of the FIFRA Scientific Advisory Panel Meeting Held July 29-30, 1998. Memorandum to M. Mulkey, Director, Office of Pesticide Programs.

Rowland, J. (1998). "DICHLORVOS (DDVP) - RE-EVALUATION - Report of the Hazard Identification Assessment Review Committee" (June 3, 1998).

Sahib, I. (1998). "Drinking Water Assessment for DDVP" (Mar. 25, 1998).

Sette, W.F. (1998). "DDVP (084001): Pathology Working Group Peer Review of 28 Day Neurotoxicity Study" (Apr. 9, 1998).

Sette, W.F. (1998). "DDVP (084001). Trichlorfon (057901). D237270: Summary Review of Published Studies on Metrifonate, a Drug Metabolized to DDVP, and Their Relevance to DDVP Risk Assessment" (MRID 44308001) (Apr. 10, 1998).

Stewart, J. (1998). "Review of Toxicity Studies on DDVP Using Human Volunteers." MRIDs 44317901, 4416201, 44248801, 44248802 (Mar. 24, 1998).

Stewart, J. (1996a). "Dichlorvos Special Studies." MRID 42880101, 42881101 (May 30, 1996).

Stewart, J. (1996b). "Review of Supplementary Pathology Data: Staging of Severity of Mononuclear Cell Leukemia Observed in Male Fisher 344 Rats in the Two Year Carcinogenicity Study." MRID 43565601 (June 20, 1996).

Stewart, J. (1996). "DDVP Transmittal of the Quantitative Risk Assessment and Response to Registrant's Questions Concerning Neurotoxicity Study and Cancer Peer Review" (Oct. 4, 1996).

Stewart and Burnam (1996). "Fifth Carcinogenicity Peer Review of Dichlorvos." Tox Chem #328. PC Code 084001 (Aug. 28, 1996).

Stewart, J. (1997). "Toxicology Branch Response to Public Comments on the PD 2/3 for Dichlorvos" (Apr. 16, 1997).

Tarplee, B. and Rowland, J. (1998). "Dichlorvos (DDVP) - Report of the FQPA Safety Factor Committee" (June 2, 1998).

* We would also like the list mentioned on page 30 (last paragraph) of the Preliminary Risk Assessment for Dichlorvos. "Therefore, the Agency has developed a list of commodities likely to be treated with DDVP that are covered by tolerances and/or Food Additive Regulations."